

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Applicant's or agent's file reference 10010012PCT | FOR FURTHER ACTION | | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/DK02/00034 | International filing date (<i>day/month/year</i>) 16.01.2002 | Priority date (<i>day/month/year</i>) 16.01.2001 | |
| International Patent Classification (IPC) or national classification and IPC ₇ A61K 31/275, 31/78, 31/785, A61P 17/00, 31/22, A61K 31/10 | | | |
| Applicant LYSTER, Hans Brinch | | | |

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|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. | This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. |
| 2. | This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. |
| | <input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). |
| | These annexes consist of a total of <u>4</u> sheets. |
| 3. | This report contains indications relating to the following items: <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application |

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Date of submission of the demand 09.08.2002 | Date of completion of this report 02.04.2003 |
| Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 | Authorized officer Gerd Strandell/EÖ Telephone No. 08-782 25 00 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/DK02/00034

I. Basis of the report**1. With regard to the elements of the international application:***

- ☐ the international application as originally filed
- ☒ the description:
pages 1-34, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☒ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages 35-38, filed with the letter of 13-01-2003
- ☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.These elements were available or furnished to this Authority in the following language english which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☒ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

| | | | |
|-------------------------------|--------|-------------|-----|
| Novelty (N) | Claims | <u>1-20</u> | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | <u>1-20</u> | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | <u>1-20</u> | YES |
| | Claims | | NO |

2. Citations and explanations (Rule 70.7)

The original claims have been amended by incorporating in new claim 1 the polymerisation of the cyanoacrylate compound upon contact with tissue fluid as described in original claim 15. New claims 2-20 correspond to original claims 2-20. Therefore, claim 15 is unnecessary and ought to be deleted.

The following documents are cited:

D1) American Journal of Ophthalmology, Volume 89,
No. 6, 1980, J.A. Fogle et al: "Tissue adhesive
Arrests stromal melting in the human cornea",
Pages 798-802

D2) WO 9325196 A1 (MEDLOGIC, INC.), 23 December 1993
(23.12.93)

D3) WO 9500153 A1 (MEDLOGIC GLOBAL CORPORATION), 5 January
1995 (05.01.95)

D4) EP 0323652 A1 (EXO VIR, INC.), 12 July 1989 (12.07.89),
Page 2, line 4 - line 48, the claims

D5) STN International, File CAPLUS, CAPLUS
accession no. 1995:354182, document no.
122:114859, Howell, Johan M. et al: "Comparison
of effects of suture and cyanoacrylate tissue
adhesive on bacterial counts in contaminated
lacerations", & Antimicrob. Agents Chemother.
(1995), 39(2), 559-60

.../...

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

D6) STN International, File CAPLUS, CAPLUS accession no. 1984:483795, document no. 101:83795, Galil, K.A. et al: "The healing of hamster skin ulcers treated with n-butyl-2-cyanoacrylate (Histoacryl blue), & J. Biomed. Mater. Res. (1984), 18(6), 601-7

D7) STN International, File CAPLUS, CAPLUS accession no. 2001:119967, document no. 135:97379, Bazell, Gregory M. et al: "Reduction mammoplasty incision closure with octyl-2-cyanoacrylate", & Surgical Forum (2000), 51, 611-613

D8) WO 9320829 A1 (MEDLOGIC, INC.), 28 October 1993 (28.10.93)

D9) WO 9747310 A1 (STOA S.A.), 18 December 1997 (18.12.97)

D10) WO 9803152 A1 (SEDERMA S.A.), 29 January 1998 (29.01.98)

D1 discloses that the direct early application of cyanoacrylate adhesive to a prepared ulcer bed and adjacent basement membrane, followed by placement of a bandage lens, gave good results in ten patients with corneal ulceration. The patients had ulceration with keratitis sicca, herpes keratitis, and other surface diseases. The cyanoacrylate application is made in order to provide structural support and to provide a barrier to tear fluid and early regenerating epithelium and thus deter the invasion of stroma. The object is to protect until reparative processes can stabilize the comprised cornea (see e.g. page 801).

D2 discloses methods for treating and/or protecting small superficial wounds, i.e. non-suturable wounds, including small cuts and abrasions. The method involves applying a cyanoacrylate adhesive onto the wound and allowing the adhesive to polymerize so as to both bind the separated skin sections and form a polymer layer over the cut. In addition to serving as a protective layer, the polymer layer also serves to promote healing and to retard infection in the cut. The cyanoacrylate adhesives rapidly polymerize in the presence of skin moisture or tissue protein. The adhesive is useful for treating wounds in an every day, typical non-sterile

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

environment. Monomeric or partially polymerized n-butyl-cyanoacrylate is a particularly preferred adhesive. The cyanoacrylate is applied to provide an effective thick coating over living tissue without diffusing into the tissue in amounts to cause irritation or necrosis of the tissue (see e.g. page 9, line 13-line 21). Applying a coating is similar to applying a plaster. Like in D1 the object is to protect. According to the present invention the object is to remove material produced in relation to a disease and to provide access to healthy tissue. However, it is not quite clear from the present claims that the cyanoacrylate is removed after polymerisation.

D3 discloses cyanoacrylate adhesives, which are useful for inhibiting formation of surface skin ulcers. The cyanoacrylate adhesives can be monomeric or partially polymeric. D3 is directed to a protective barrier for preventing the skin from direct frictional contact with any other surface. D3 does not provide any hints of removing necrotic material. Instead D3 is concerned with inhibiting surface skin ulceration and therefore with the prevention of developing of such necrotic material.

D4 discloses cosmetic treatment of facial skin for the removal of materials, including bacteria, fungi, mites, and follicular horn, from the surface and the sebaceous follicles of human skin by applying a coating or film of liquid polymerizable cyanoacrylate adhesive. The coating of polymerized adhesive with the attached materials is removed from the skin. As may be clear from page 4, line 7-line 8 post-treatment redness may appear. The liquid cyanoacrylate adhesive is brushed or coated or applied onto the skin, after the skin has been prepared by washing and drying (see e.g. page 3, line 9-line 10). This is in direct contrast to the present invention in which tissue fluid is utilized for the specific inventive polymerisation.

D5 discloses that wounds closed with cyanoacrylate adhesive alone had lower staphylococcal counts than wounds containing suture material.

D7 discloses that the use of octyl-2-cyanoacrylate to close large reduction mammoplasty incisions is a safe method.

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

Thus, D5 and D7 relate to closing wounds in direct contrast to the present invention, which relates to opening wounds. When wounds are glued together with cyanoacrylate adhesive it is very important that the wound is as dry as possible. Residues of blood and serum serve as a substrate for bacterial growth. This risk should be avoided or kept at a minimum. Nor is the cyanoacrylate removed after polymerisation and gluing but remains in place in the glued wound.

D6 discusses the healing of hamster skin treated with n-butyl-2-cyanoacrylate. D6 discloses that n-butyl-2-cyanoacrylate decreased the inflammatory exudates early in the experiment, and epithelial migration occurred slightly earlier in experimental tissue. The wounds are new (that is, not wounds that may require revision) and the treatment is solely for preventing infection of the wound.

D8 discloses the use of cyanoacrylate adhesives to serve as a callus for retarding blister formation. The cyanoacrylate adhesive is applied to the skin areas prone to blistering either prior to or during physical activities but prior to blister formation. This action is similar to applying a protective plaster.

D9 and D10 disclose the use of a glyceryl poly(meth)acrylate gel for treating or preventing different skin disorders, such as viral (herpes) diseases, candidoses, varicose ulcers, and scars.

None of the cited documents has explicitly disclosed the claimed invention. According to the applicant the advantages of the claimed invention are for example that a hyperkeratotic area, wet eczema and/or running sore are removed and cleaned and the remaining "wounds or ulcers" are able to heal fast and upon a normal tissue basis. Moreover the post treatment is reduced considerably. The effects are demonstrated in the examples of the present application. The achieved effect is not obvious to a person skilled in the art.

Consequently, the invention claimed in claims 1-20 is novel, and is considered to fulfil the requirements inventive step, and industrial applicability.

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VI. Certain documents cited

1. Certain published documents (Rule 70.10)

| Application No. Patent No. | Publication date (day/month/year) | Filing date (day/month/year) | Priority date (valid claim) (day/month/year) |
|-------------------------------|--------------------------------------|---------------------------------|-------------------------------------------------|
| US 20010051179 A1 | 13.12.2001 | 14.03.1997 | 20.09.1996 |
| WO 0112243 A1 | 22.02.2001 | 11.08.2000 | 12.09.1999 |

2. Non-written disclosures (Rule 70.9)

| Kind of non-written disclosure | Date of non-written disclosure (day/month/year) | Date of written disclosure referring to non-written disclosure (day/month/year) |
|--------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------------|
|--------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------------|

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 02/00034

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/275, A61K 31/78, A61K 31/785, A61P 17/00, A61P 31/22, A61K 31/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| P,X | US 2001/0051179 A1 (BERMAN), 13 December 2001 (13.12.01) | 1-20 |
| | -- | |
| P,X | WO 0112243 A1 (CLOSURE MEDICAL CORPORATION), 22 February 2001 (22.02.01) | 1-20 |
| | -- | |
| X | American Journal of Ophthalmology, Volume 89, No. 6, 1980, J.A. Fogle et al: "Tissue adhesive arrests stromal melting in the human cornea", pages 798-802 | 1-20 DA |
| | -- | |
| X | WO 9325196 A1 (MEDLOGIC, INC.), 23 December 1993 (23.12.93) | 1-20 J2 |
| | -- | |

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

3 April 2002

Date of mailing of the international search report

22 -04- 2002

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 02/00034

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | WO 9500153 A1 (MEDLOGIC GLOBAL CORPORATION), 5 January 1995 (05.01.95) -- | 1-20 D3 |
| X | EP 0323652 A1 (EXO VIR, INC.), 12 July 1989 (12.07.89), page 2, line 4 - line 48, the claims -- | 1-20 D4 |
| X | STN International, File CAPLUS, CAPLUS accession no. 1995:354182, document no. 122:114859, Howell, Johan M. et al: "Comparison of effects of suture and cyanoacrylate tissue adhesive on bacterial counts in contaminated lacerations", & Antimicrob. Agents Chemother. (1995), 39(2), 559-60 -- | 1-20 D5 |
| X | STN International, File CAPLUS, CAPLUS accession no. 1984:483795, document no. 101:83795, Galil, K.A. et al: "The healing of hamster skin ulcers treated with n-butyl- 2-cyanoacrylate (Histoacryl blue), & J. Biomed. Mater. Res. (1984), 18(6), 601-7 -- | 1-20 D6 |
| X | STN International, File CAPLUS, CAPLUS accession no. 2001:119967, document no. 135:97379, Bazell, Gregory M. et al: "Reduction mammoplasty incision closure with octyl-2-cyanoacrylate", & Surgical Forum (2000), 51, 611-613 -- | 1-20 D7 |
| X | WO 9320829 A1 (MEDLOGIC, INC.), 28 October 1993 (28.10.93) -- | 1-20 D8 |
| A | WO 9747310 A1 (STOA S.A.), 18 December 1997 (18.12.97) -- | 1-20 D9 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 02/00034

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------|-----------------------|
| A | <p>✓ WO 9803152 A1 (SEDERMA S.A.), 29 January 1998 (29.01.98)</p> <p>-----</p> | <p>1-20 010</p> |

INTERNATIONAL SEARCH REPORT
Information on patent family members

28/01/02

International application No.
PCT/DK 02/00034

| Patent document cited in search report | | | Publication date | Patent family member(s) | | Publication date |
|----------------------------------------|--|--|------------------|-------------------------|----------|------------------|
| US 2001/0051179 A1 | | | 13/12/01 | NONE | | |
| WO 0112243 A1 | | | 22/02/01 | AU 6637800 A | 13/03/01 | |
| | | | | US 6310166 B | 30/10/01 | |
| WO 9325196 A1 | | | 23/12/93 | AU 4032993 A | 18/11/93 | |
| | | | | AU 4630693 A | 04/01/94 | |
| | | | | US 6342213 B | 29/01/02 | |
| | | | | WO 9320828 A | 28/10/93 | |
| WO 9500153 A1 | | | 05/01/95 | AU 7178094 A | 17/01/95 | |
| | | | | EP 0707483 A | 24/04/96 | |
| | | | | US 5403591 A | 04/04/95 | |
| EP 0323652 A1 | | | 12/07/89 | SE 0323652 T3 | | |
| | | | | AT 69161 T | 15/11/91 | |
| | | | | DE 3866098 D | 00/00/00 | |
| | | | | ES 2026990 T | 16/05/92 | |
| | | | | GR 3003641 T | 16/03/93 | |
| | | | | US 4752472 A | 21/06/88 | |
| WO 9320829 A1 | | | 28/10/93 | AU 4032993 A | 18/11/93 | |
| | | | | AU 4033093 A | 18/11/93 | |
| | | | | US 5306490 A | 26/04/94 | |
| | | | | WO 9320828 A | 28/10/93 | |
| WO 9747310 A1 | | | 18/12/97 | AU 6309296 A | 07/01/98 | |
| | | | | BR 9610211 A | 21/12/99 | |
| | | | | EP 0843556 A | 27/05/98 | |
| | | | | JP 11511180 T | 28/09/99 | |
| WO 9803152 A1 | | | 29/01/98 | AU 6704396 A | 10/02/98 | |